Summary of RotaTeq® Vaccine Reports to VAERS, 3/1/06-6/14/07

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Acknowledgement

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Outline

- Reports to the Vaccine Adverse Event Reporting system (VAERS)
- Update:
  - Vaccine Safety Datalink (VSD) study
  - Merck phase 4 study
- Data interpretation

VAERS RotaTeq® reports

- 6.2 million doses distributed (March 2006- May 31, 2007)*
- From March 1st, 2006 – June 14, 2007 VAERS received total of 1,251 reports following RotaTeq vaccination
  - Rotateq alone: 573 (46%)
  - 1st dose: 609 (47%)
  - Most frequently reported outcomes: diarrhea, vomiting, fever and haematochezia

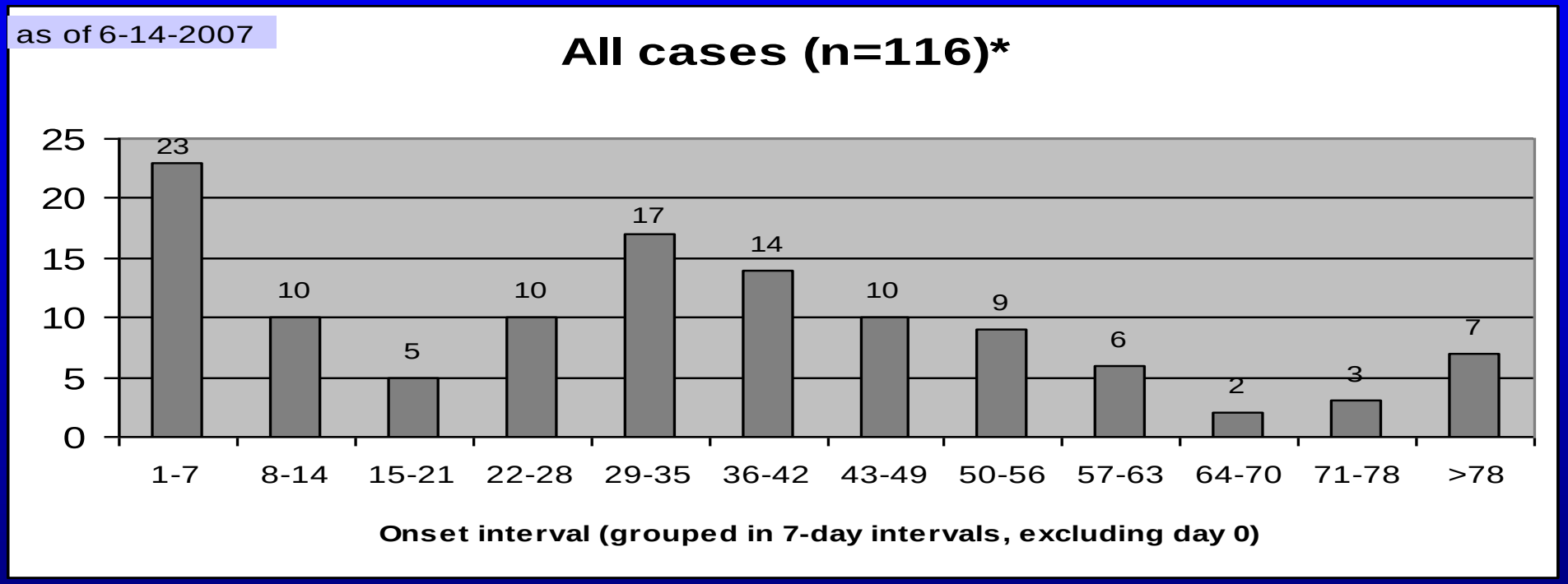
* Merck personal communication

VAERS Intussusception (IS) Reports* after RotaTeq® Vaccine

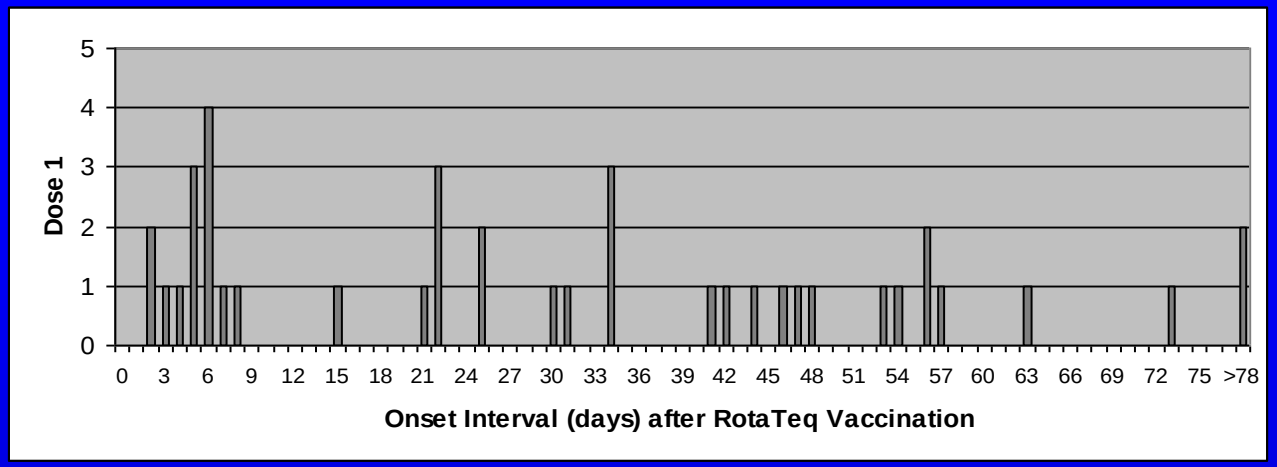
- 117 (9.4%) confirmed Intussuception (IS) reports
  - 38 reports 1-21 days after vaccination
  - 23 of 38 were within 1-7 days
- No intussusception deaths reported

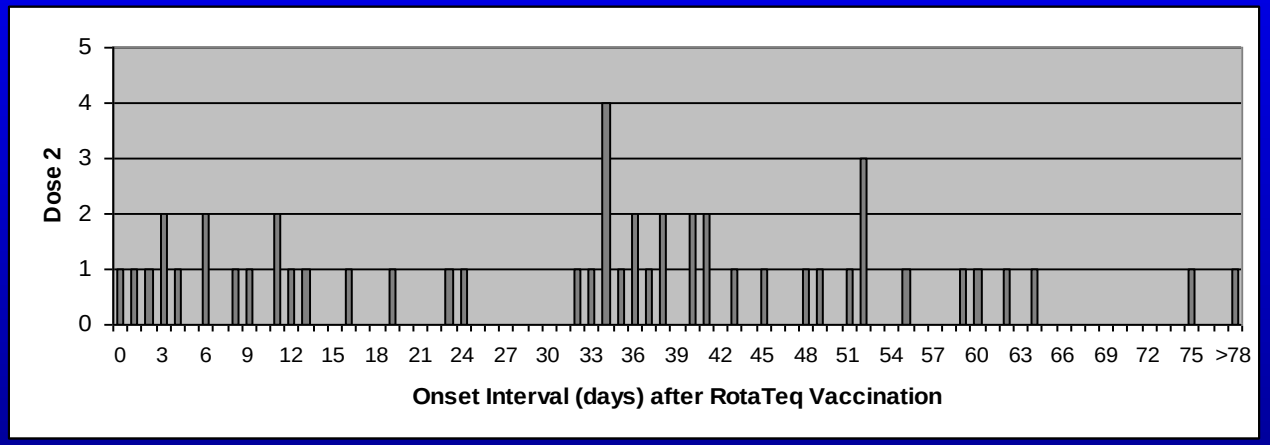
* Based on Brighton case definition –level 1

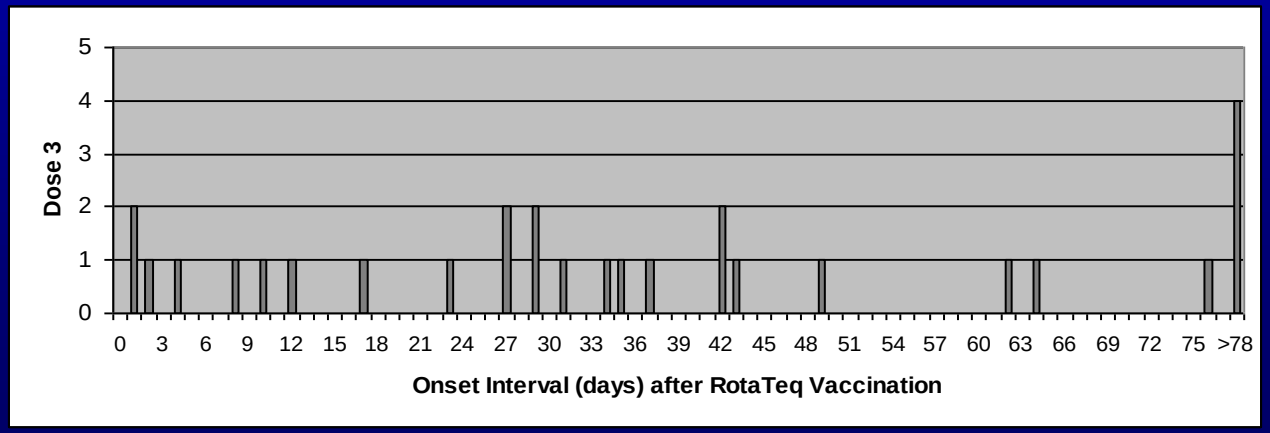
RotaTeq®
IS Reports to VAERS by Onset-Interval (N=116)*



*excludes one report on day zero







IS Reports by Dose

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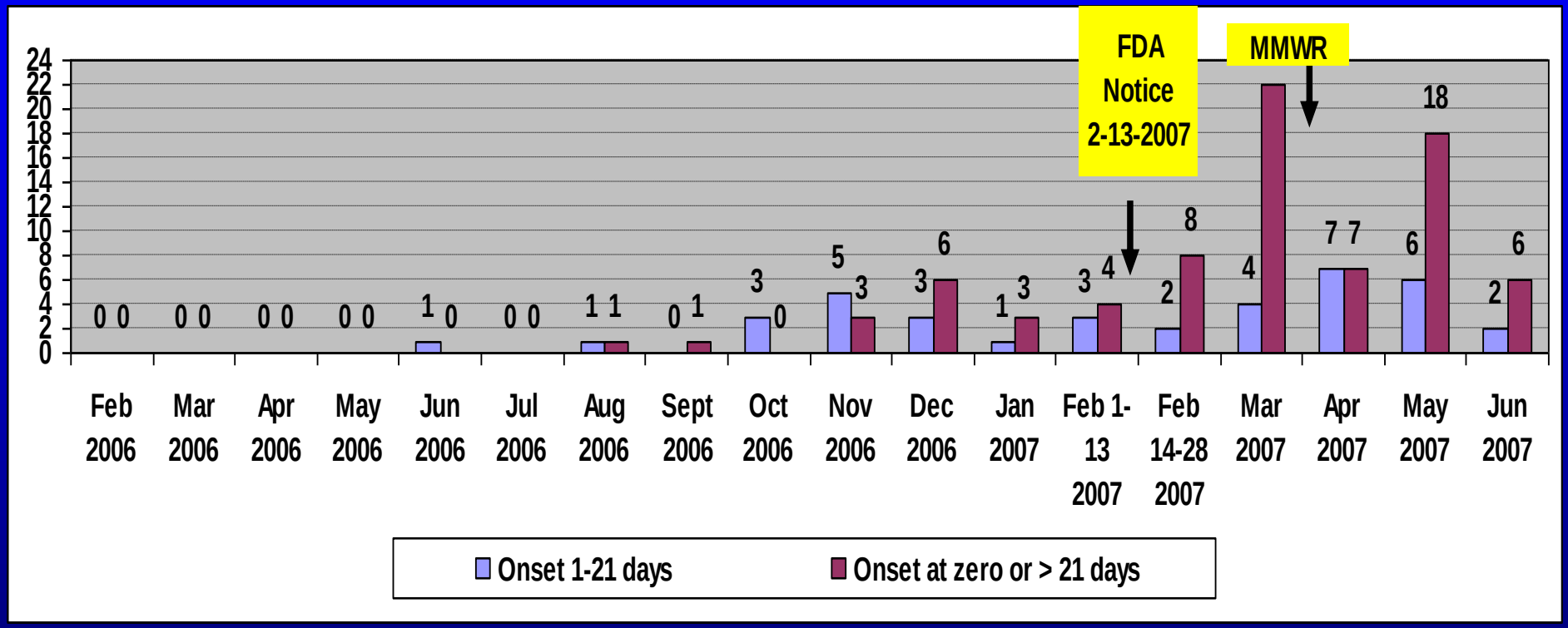
IS reports as of June 14, 2007



Epidemiology of IS reports

- Mean age at symptom onset was 23 weeks
  - Range 9-45 weeks
- 43% Male; 46% Female; 11% gender not reported
- 57 (49%) contrast enema
- 37 (32%) surgical reduction
- 19 (16%) surgical resection
- 2 (2%) spontaneous resolution
- 2 (2% unknown

Rotateq® IS Data from Vaccine Safety Datalink (VSD)

- From May 21, 2006 through June 17, 2007:
- Total of 68,858 vaccinations given
  - No reports of intussusception within 30 days of vaccination

Update on VSD Rapid Cycle* (June 17, 2007)

Age Group	Dose 1	Dose 2	Dose 3	Total
0-6 Weeks	25	0	0	25
6-14 Weeks	31,155	172	0	31.327
15-23 Weeks	1,411	20,559	41	22,013
24-35 Weeks	635	1,564	13,045	15,244
36-52 Weeks	39	29	88	156
NA	91	1	1	93
Total	33,356	2,325	13,177	68,858

*Data from 6 sites; Dose 1 48%; dose 2 33% & Dose 3 19%

Merck RotaTeq® Post-licensure Safety Study*

- **Prospective observational active surveillance**
- **Study population:** large insured U.S. population
  - Annual birth cohort ~100,000
  - Planned final study size: 44,000 vaccinated children
- **Study plan:** Monitor rates of IS and overall vaccine safety
  - Compare rates to several control groups
  - 30 days post vaccination for each dose

*source: Merck unpublished data , 6/13/07

Merck RotaTeq® Post-licensure Safety Study* (Cont.)

- **Update: 7,196 RotaTeq® recipients through 3rd quarter of 2006**
  - **Follow-up through December 31, 2006 no case of intussusception in Rotateq recipients**
  - **3 cases in controls (n=14, 310) RR=0.5, 95%CI: 0.01 - 4.75**

- **next review**
  - **~18,000 RotaTeq® recipients vaccinated February 2006 through December 2006**
  - **Follow-up through March 31, 2007**

***source: Merck unpublished data , 6/13/07**

Data Interpretation

Do the Observed Number of Intussusception Cases Exceed Expected?

- Observed versus expected calculations
  - Age-stratified because baseline intussusception rate varies 10-fold during 1st six months of life
  - Data assumptions
- Sensitivity Analysis
  - Reporting completeness to VAERS
  - Number of vaccine doses administered
- Unanswered questions and next steps

Observed versus Expected 1 to 21 Days* (any dose)

Age Group	VAERS Cases	Expected Cases*
6-14	14	30
15-23	14	36
24-35	10	33
Total	**38**	**99**

Exact Poisson—Stratified by age group

Rate Ratio	Lower 95% CL	Upper 95% CL	P-Value
0.37	0.24	0.56	<0.001

Data assumptions:

--100% VAERS reporting completeness

--100% distributed doses administered

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***** *Source: VSD for background and age of vaccine administration; Merck distribution data*

Observed versus Expected 1 to 7 Days* (any dose)

Age Group	VAERS Cases	Expected Cases*
6-14	10	10
15-23	9	12
24-35	4	11
Total	**23**	**33**

Exact Poisson—Stratified by age group

Rate Ratio	Lower 95% CL	Upper 95% CL	P-Value
0.67	0.40	1.08	<0.10

Data assumptions:

--100% VAERS reporting completeness

--100% distributed doses administered

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** Source: VSD for background and age of vaccine administration; Merck distribution data*

RotaTeq Dose 1 (1 to 7 Days*)

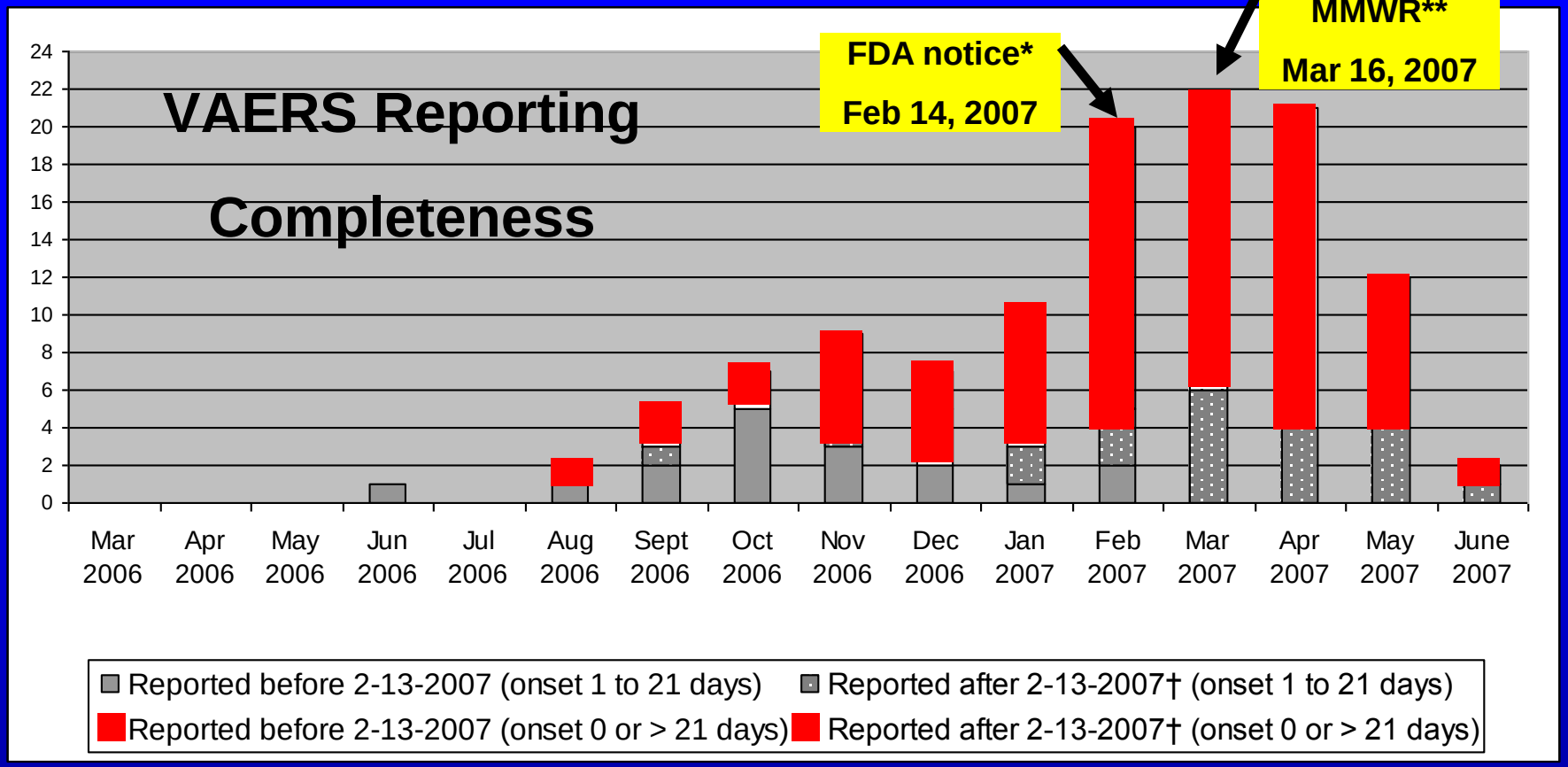
VSD
93% dose 1 administered

Age Group (weeks)	VAERS Cases	Expected Cases*
6-14	10	10
15-23	2	1
24-35	0	0.5
Total	**12**	**12**

- ***Rotashield Dose 1 experience**:***
  - 80% of the reported VAERS intussusception cases were after dose 1
    - (vs. 34% RotaTeq)
  - 80% administered > 90 days of age
    - (vs. 7% RotaTeq)
  - 37-fold risk within 3-7 days of vaccination

*** 100% reporting and 100% distributed doses administered;**

****Murphy et al. 1999 NEJM**
****Zanardi et al. 2001**
****Murphy et al. 2003 JID**



- Suspected to be high within 1-21 days of vaccination
  - 68% of reported IS cases to VAERS > 21 days post-vaccination
  - Majority of reports after FDA notification and MMWR were greater than 21 days since vaccination

*available at http://www.fda.gov/cber/safety/phnrota021307.htm

**CDC; MMWR 2007; 56(10);218.

Data Assumptions: Vaccine administration

- What proportion of doses distributed are actually administered?
- Factors favoring vaccine uptake
  - ~ 400,000 doses distributed per month
  - VFC contract in place since July 2006—purchases vaccine for nearly 50% of US children
- Rotashield experience
  - National Immunization Survey*: 66% of distributed doses administered

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* Smith et al. Pub Hlth Rep 2003

Sensitivity Analysis*

ASSUMPTIONS

75% reporting to VAERS

75% of distributed doses are administered

	VAERS Cases	Expected Cases*	RR (95% CL)
1 – 21 days	54	74	0.70 (0.48 – 1.01)
1 – 7 days	30	25	1.15 (0.72– 1.8)

ASSUMPTIONS

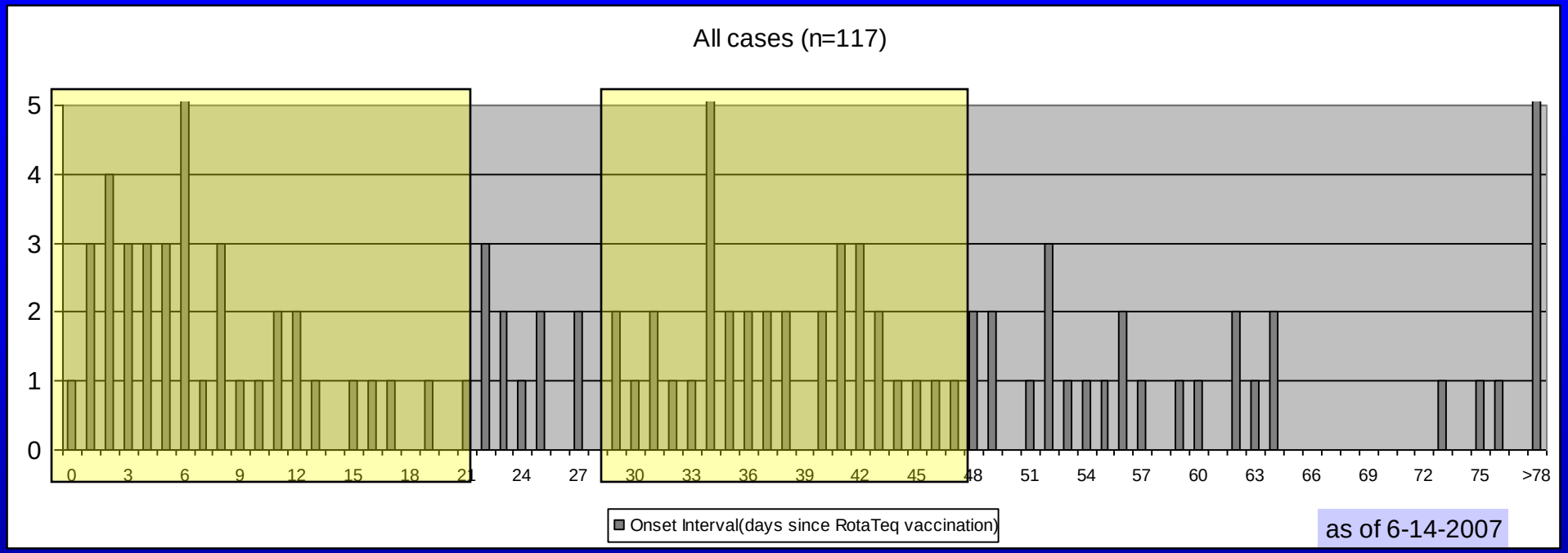
50% reporting to VAERS

50% of distributed doses are administered

	VAERS Cases	Expected Cases*	RR (95% CL)
1 – 21 days	76	50	1.47 (1.05 – 2.06)
1 – 7 days	46	17	2.61 (1.76– 3.84)

* *Source: VSD for background and age of vaccine administration; Merck distribution data*

Other Observations



- Clustering effect:
  - Passive surveillance: reporting better closer to event
  - Cannot exclude small risk
  - 2nd clustering also suggests week 1 clustering could be a random phenomenon
- Keep in mind, numbers are small

Summary observations

- Combined safety data without signal
  - 105,000 doses pre-licensure clinical trial
  - 68,858 VSD post-licensure doses
  - 7,196 doses Merck post-licensure study
  - 16 months VAERS data

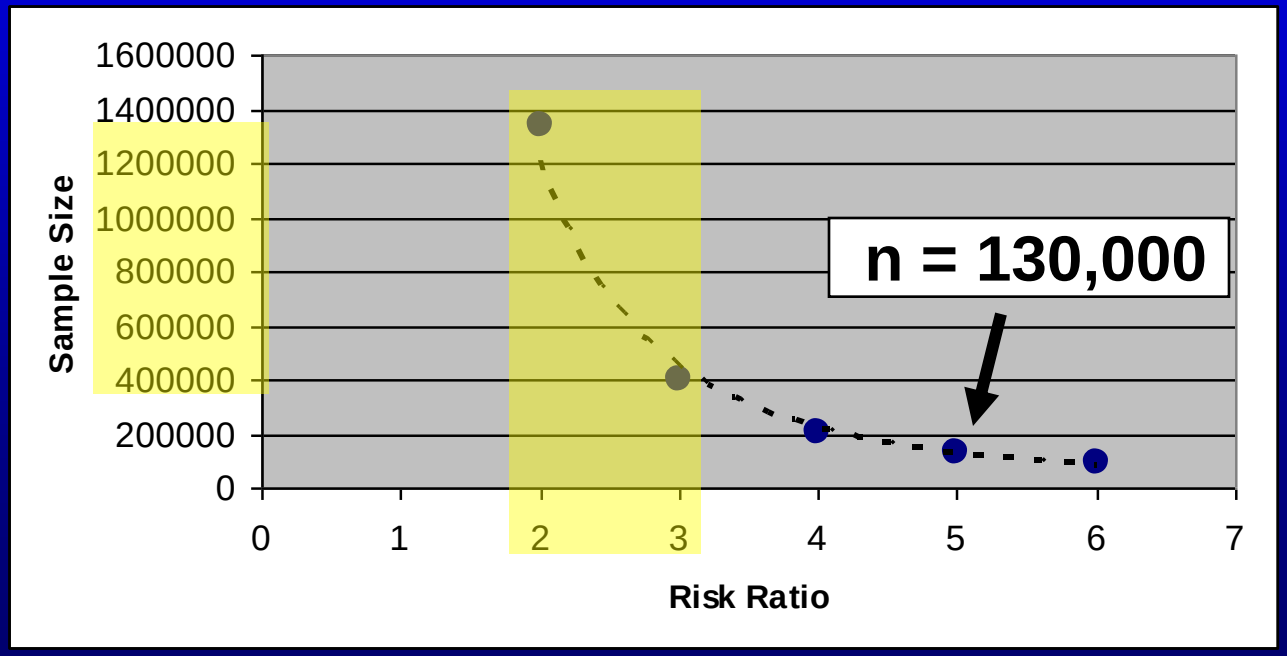
- Cannot rule out small increased risk and need ongoing monitoring

Post-licensure cohort sample size

Risk window: 7 days of dose 1 vaccination

Risk ratio	Sample Size
2	1.3 million
3	400,000

Attributable cases*	Rotavirus hospitalizations
25	50,000 to 70,000 (20 to 60 deaths)
50	



* Assumption: entire US birth cohort (~4 million) were vaccinated with dose 1 of a rotashield vaccine

Conclusion and Next Steps

- Observed intussusception rates are not greater than expected
  - interpreted with limitations of passive surveillance
- Ongoing monitoring, particularly during 1st week after vaccination
- Continue to follow VSD and Merck post-licensure cohorts
  - Will need large cohort to exclude smaller risk

Extra slides

Epidemiology of IS reports 1-21 days post-vaccination

- Total of 38 (32.4%) reports
- Mean age at symptom onset was 19 weeks

- 19 (50%) had contrast enema
- 11 (29%) surgical reduction
- 8 (21%) surgical resection

Brigthon Collaboration Case Definition for IS

Level 1

Surgical criteria AND/OR
Radiological criteria AND/OR
Autopsy criteria

Level 2

Clinical criteria
2 major OR 1 major & 3 minor criteria

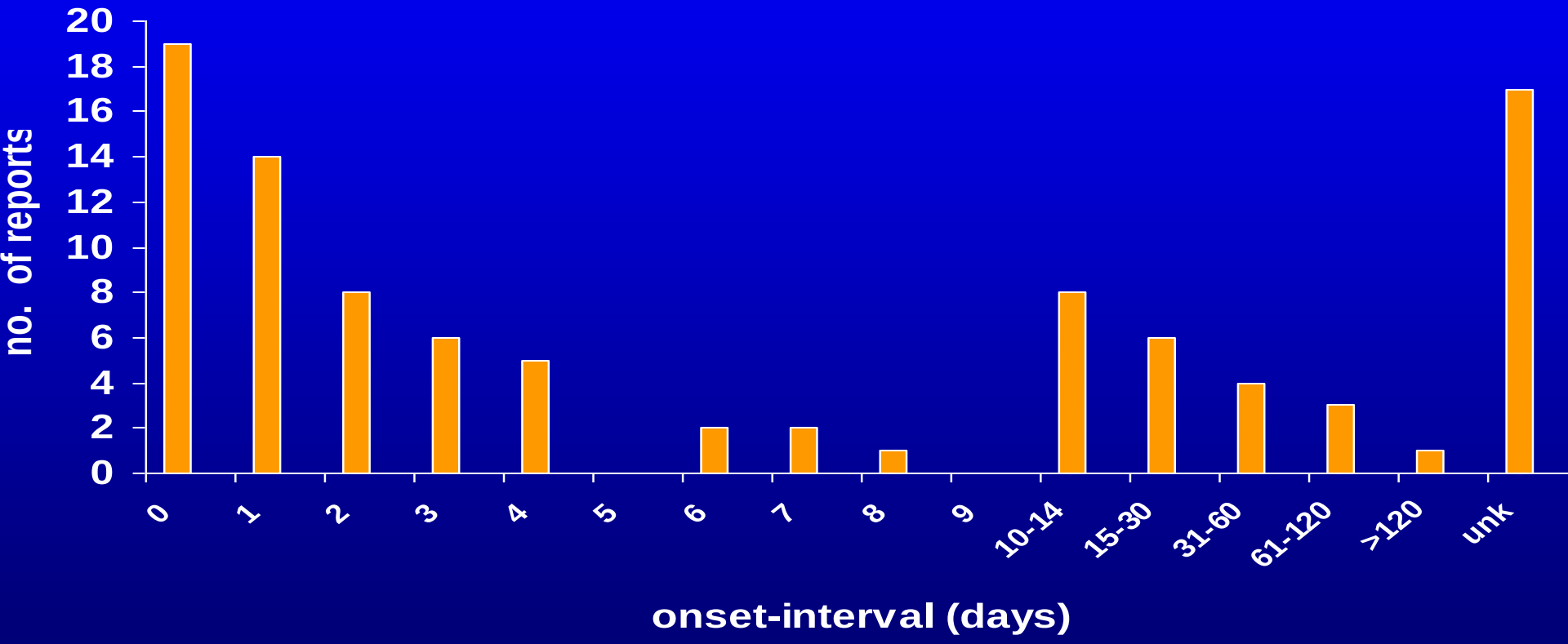
Level 3

Clinical criteria
> 4 minor criteria

Rotateq® IS Data from Vaccine Safety Datalink (VSD)

- Total of 147,107 all other vaccines
- 2 intussusception reports within 30 days of vaccination

Haematochezia Reports following RotaTeq™ Vaccine to VAERS by Onset-Interval (N=96)*



Haematochezia Reports following RotaTeq™ Vaccine to VAERS*

- Since March 2007 through June 14, 2007 VAERS received 95 reports following RotaTeq vaccine
- 15 (15.6%) were serious report
- 43(45%) after single RotaTeq vaccine
- 53 (55%) reports in children 2 month of age

*Excluding IS reports